American Journal of Hematology 54:170–177 (1997)

LETTERS AND CORRESPONDENCE

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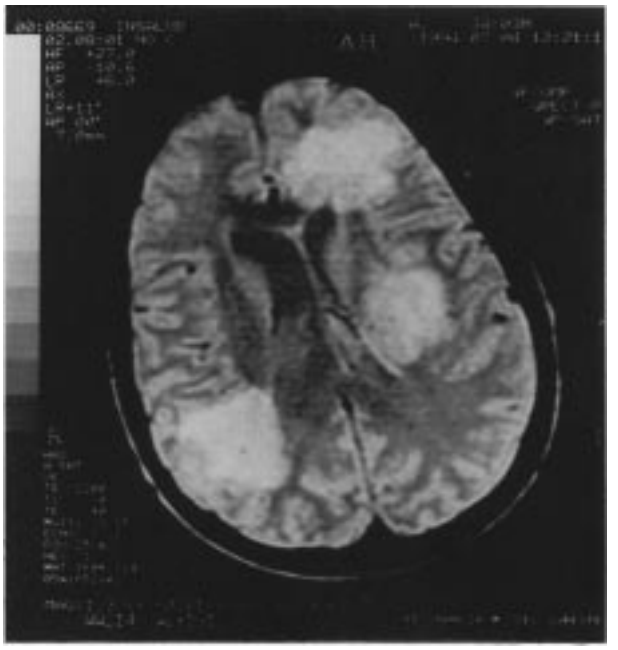

Fig. 1. Axial MRI showing many lesions in both hemispheres. High-intensity signal on T2, with a moderate surrounding edema and effect of mass.

Disseminated Aspergillosis After Mobilization With Intensive Chemotherapy Prior to Autologous Stem-Cell Transplant in Chronic Myeloid Leukemia

To the Editor: Autologous transplantation with stem cells mobilized after intensive chemotherapy may achieve Ph-negative hemopoiesis in patients with chronic myeloid leukemia (CML), and this may prolong survival [1]. However, this procedure is not without risks. We report on a case of disseminated *Aspergillus flavus* infection during the protracted period of neutropenia following mobilization.

A 34-year-old male was diagnosed in December 1991 with Ph-positive chronic-phase CML. The patient received hydroxiurea throughout his disease, except for a 7-month trial with interferon without any response. After an unsuccessful search for an HLA-identical donor, the patient was proposed for ASCT 40 months from his diagnosis.

With the aim of mobilizing Ph-negative peripheral stem cells (PSC), the patient received cytarabine, 300 mg/m^2/days 1–5, mitoxantrone 12 mg/m^2/days 1–3, and etoposide 150 mg/m^2/days 1–3. G-CSF (8.8 μg/kg/day) was given from absolute neutrophil count (ANC) $<1.5 \times 10^9$/l, and the leukaphereses were planned when the absolute white blood cell count exceeded 1×10^9/l. Ciprofloxacin and fluconazole were used as prophilaxis against infection. The time of ANC $<0.5 \times 10^9$/l lasted 30 days (days 8–38), and the nadir was 0 during 16 days.

On day 21, the patient developed fever and dry cough. Physical examination showed erythema in the catheter exit site, and left lung sibilants. CXR was normal. *Streptococcus mitis* grew from blood cultures. He was started on imipenem and vancomycin, and subsequent blood cultures were negative but symptoms persisted. On day 26, bronchoalveolar lavage (BAL) disclosed fungal elements in the gram-stain. Although cultures were negative, amphotericin B (1 mg/kg/day) was added. In the following days, despite granulocyte recovery, he developed an interstitial pneumonitis that precluded the leukoapheresis procedure. A new BAL and transbronchial biopsy were uninformative. On day 47, the patient presented with right hemiparesis and seizures. Cerebrospinal fluid study was negative. MRI showed many lesions in both cerebral hemispheres (Fig. 1). On day 50, a maculopapular rash with a few subcutaneous nodules was noted. Skin biopsy revealed a septal panniculitis, and its culture grew *Aspergillus flavus.* In spite of adding flucitosine, the neurological condition of the patient deteriorated and he died on day 66. Postmortem examination was not allowed.

ASCT is an alternative therapy for patients with CML who lack an HLA-identical donor [2]. PSC collected during early recovery from intensive chemotherapy may be Ph- and even PCR-negative. Using this material, Carella et al. [1,3] have shown that some patients might achieve a sustained Ph-negative hemopoiesis after ASCT. However, this potential benefit must be carefully weighed against the risk of treatment-associated mortality. The Italian Group [1] observed an 8% mortality after transplant in patients who failed to engraft, but there are no clear data about mobilizations's related mortality. With a similar approach, Kantarjian et al. [4] reported a 7% mortality for mobilization chemotherapy.

Our patient had a 30-day period of profound neutropenia, during which he developed a fatal disseminated aspergillosis by *A. flavus.* This filamentous fungus is ubiquitous, and caution is necessary in the evaluation of its isolation. However, its identification in skin culture (based on morphological criteria: conidiophores of biseriate) along with clinical evolution is highly suggestive of this diagnosis. [5].

In conclusion, our case illustrates a risk of life-threatening fungal infection associated with these innovative therapies. This emphasizes the need for launching randomized trials in order to show survival advantages in comparison with more conventional therapeutic approaches.

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Interleukin-6 and Cancer-related Hypoaldosteronism

To the Editor: Recently, the new endocrinological function of interleukin-6 (IL-6) was reported by Chung et al. [1]. They hypothesized that secretion of IL-6 by tumors was responsible for hypoaldosteronism in patients with cancer. They presented 3 patients with unexplained hyperkalemia, hypoaldosteronism, *and* high plasma IL-6 concentration among 82 patients with various cancers. However, plasma IL-6 levels in the remaining 79 patients were not described.

Castleman's disease [2] is a rare lymphoproliferative disorder with high levels of plasma IL-6 [3]. However, hypoaldosteronism or hyperkalemia in patients with Castelman's disease has not been reported. To clarify the association of elevated IL-6 and hypoaldosteronism, we measured serum levels of aldosterone and plasma renin activity in 2 patients with Castleman's disease. Patients' clinical characteristics and laboratory data are summarized in Table I. Both patients had high levels of C-reactive protein (CRP), hyper-γ-globulinemia, and extremely elevated serum IL-6. However, their serum potassium remained in normal range over 2 years after diagnosis. Moreover, patient 1 had a normal serum aldosterone concentration and normal plasma renin activity. Patient 2 had a slightly reduced serum aldosterone concentration and elevated plasma renin activity. Their normal serum cortisol levels suggest that they are free from adrenal insufficiency. There was no elevation of plasma adrenocorticotropin (ACTH) in either patient. Thus it was thought that the mild hypoaldosteronism in patient 2 was not induced by the elevated ACTH level [4]. Although it is still possible that she has true hyperreninemic hypoaldosteronism without hyperkalemia, these findings imply that high levels of serum IL-6 alone do not cause hyperkalemia and hypoaldosteronism in patients with Castleman's disease. Serum IL-6 levels of these 2 patients are considerably higher than those of 3 patients described by Chung et al. [1]. Hence it seems that hypoaldosteronism in their patients was caused by other factors than elevated plasma IL-6, e.g., metastasis to the adrenal glands [5]. Moreover, the IL-6 concentrations that they used in in vitro experiments were extremely higher than the plasma levels of their patients; therefore, it is not clear that IL-6 truly inhibits the secretion of aldosterone by adrenal tissue in vivo.

Considering these findings, we conclude that hyperkalemia and hypoaldosteronism in patients with cancer is not explained by high levels of serum IL-6 alone.

TABLE I. Characteristics of Two Patients With Castleman's Disease*

	Patient 1	Patient 2	Normal range
Age (years)	59	26	
Sex	Male	Female	
CRP (mg/dl)	2.8	12.9	<0.5
γ-globulin (g/dl)	5.6	7.0	0.65–1.70
Serum potassium (mEq/l)	3.8	4.0	3.3–5.0
Serum creatinine (mg/dl)	0.7	0.5	0.5–1.5
Basal serum aldosterone (pg/ml)	100	28	35–240
Basal plasma renin activity (ng/ml/hr)	0.9	7.0	0.3–2.9
Serum cortisol (μg/dl)	8.2	9.3	4.0–18.3
Plasma ACTH (pg/ml)	5	6	9–52
Serum interleukin-6 (pg/ml)	>1,000	405	<4.0

*CRP, C-reactive protein; ACTH, adrenocorticotropin.

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Plasma Protein Z Levels in Early Respiratory Distress Syndrome

To the Editor: Disseminated intravascular coagulation (DIC) is frequently encountered in preterm infants with advanced respiratory distress syndrome (RDS) [1]. However, we previously reported normal plasma fibrinogen, antithrombin III, protein C, tissue plasminogen activator [2], thrombin/antithrombin III complex (TAT), and prothrombin fragment 1.2 (F1.2) [3], but lower D-dimer and higher plasminogen activator inhibitor (PAI) [2]

TABLE I. Plasma Protein Z Levels in Preterm Infants With or Without Respiratory Distress Syndrome (Mean ± SD)

	Controls (n = 20)	Infants with RDS (n = 17)
Gestational age (weeks)	30.9 ± 2.6	30.7 ± 2.8
Body weight (g)	1425 ± 330	1520 ± 683
Protein Z (μg/ml)	0.28 ± 0.14	0.34 ± 0.20

and von Willebrand antigen (vWF-Ag) levels [4] within the first few hours of life in preterm infants who developed RDS compared to the control group. According to these findings, DIC is not a prominent event in early (or developing) RDS. Higher D-dimer, PAI, and vWF-Ag levels are probably related to abnormalities in the fibrinolytic system due to lung damage and local platelet activation in RDS. These changes in the lung may cause abnormalities in coagulation other than DIC. Therefore, we studied plasma protein Z levels in preterm infants who developed RDS within the first few hours of life to evaluate the hemostatic system in detail.

The physiological function of protein Z, which is a vitamin K-dependent protein, is still unknown. The observation that thrombin associates with phospholipid surfaces in the presence of bovine protein Z has prompted the suggestion that this phenomenon may provide a mechanism whereby thrombin is kept from diffusing into the vascular lumen and away from the site of injury [5–7]. However, approximately tenfold higher concentrations of human protein Z are required to bind an equivalent amount of thrombin as can be bound with bovine protein Z. Therefore, considering the in vivo concentrations of protein Z, it seems unlikely that protein Z would perform this function to any significant extent in humans [8].

We previously reported normal plasma protein Z levels within the first few hours of life in preterm infants compared to full-term infants [9]. In this study, we evaluated plasma protein Z levels in 37 preterm infants who did or did not develop RDS. Blood samples for protein Z testing were obtained from a peripheral vein within 6 hr after birth before routine vitamin K1 prophylaxis, and were mixed with 3.8 trisodium citrate according to their hematocrit levels. The tubes were centrifuged at approximately 3,000 rpm for 10 min within 30 min of collection. The plasma was stored at −20°C for <1 month before the procedure. Human protein Z was isolated according to Miletich and Broze [10] (ELISA method, Asserchrom Protein Z; Diagnostica Stago, Asnieres-Sur-Seine, France).

Among 37 preterm infants, 20 infants in stable clinical condition served as control group. Seventeen infants developed RDS, which was considered to be present if all the following criteria were fullfilled: symptoms of respiratory distress within 1 hr after birth and present for at least 24 hr, respiratory support, including mechanical ventilation, and typical findings on lung radiography and arterial blood gas analysis. None of the infants with RDS had other diseases. All data were expressed as mean ± SD. The Mann-Whitney U-test was used to search for significant differences in comparing healthy infants with the patient group.

There were no significant differences in mean gestational ages and birth weights between groups (30.9 ± 2.6 weeks vs. 30.7 ± 2.8 weeks, and 1,425 ± 330 g vs. 1,520 ± 683 g, respectively; $P > 0.05$). Mean plasma protein Z levels were found to be similar in the two groups (0.28 ± 0.14 μg/ml vs. 0.34 ± 0.20 μg/ml; $P > 0.05$) (Table I).

According to these findings, there is no abnormality in plasma protein Z in developing RDS. To the best of our knowledge, plasma protein Z levels in infants with RDS have not been reported previously. The accumulated findings from different centers in the literature would be useful in reaching a reliable conclusion concerning plasma protein Z levels in newborn infants.

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Danazol in Refractory Pruritus of Myeloproliferative Disorders

To the Editor: We read with interest the paper by Kolodny et al. [1] reporting the efficacy of danazol in treating refractory pruritus in 8 patients affected with myeloproliferative disorders. Severe pruritus may be a cause of severe discomfort in patients with myeloproliferative disorders, in particular in those affected with polycythemia vera, and several drugs have been used unsuccessfully. An effective drug for these patients is needed. However, the authors do not give information about blood cell count before and after treatment with danazol, and we wonder whether potentially dangerous increases could have occurred as a side effect of therapy. In fact, hemoglobin and hematocrit usually rise during treatment with androgens [2] and, although in the different conditions of idiopathic thrombocytopenic purpura (ITP) and myelodysplasia, elevation in platelet and leukocyte counts can also be observed after danazol administration. In ITP the rise in platelet count seems to be related to an immunomodulating activity of the drug [3], while in myelodysplasia the mechanism has not been clearly elucidated and it is possible that danazol partially corrects the defective hematopoiesis [4].

Such effects would be potentially catastrophic in myeloproliferative disorders, in which cytoreduction is often warranted. The authors seem aware of this, and in fact the use of busulfan is reported in the representative case study. However, the effect of busulfan plus danazol was not detailed, and we feel that adequate caution and information are needed prior to new therapeutical recommendations.

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Bulky Plasmacytoma of the Skull With Intracranial Involvement

To the Editor: We read with great interest the letter by Alegre et al. [1] reporting a myeloma case presenting as plasmacytoma of the base of the skull. We would like to present an additional case of plasmacytoma of the skull, which was bulky and associated with intracranial involvement causing neurological symptoms during the clinical course of multiple myeloma.

A 52-year-old man was admitted to our hospital with complaints of diplopia and a rapidly progressive painful protruding mass on his head. He had been followed for IgG-κ secreting multiple myeloma for 4-years and had received multiple chemotherapy regimens such as melphalan-prednisone, vincristine-adriamycin-dexamethasone, and interferon. Local radiotherapy had been applied to his vertebral lytic lesions. The disease had been followed with partial remissions and relapses since then. Physical examination of the patient revealed a tender 11 × 9 cm protruding mass on the left parietooccipital region of the skull and an abduction limitation of the left eye. A large osteolytic lesion in the parietooccipital bone and several punched-out lesions in other cranial bones were evident in the skull X-ray. Cranial contrast-enhanced T1-weighted magnetic resonance images of the head showed an extraaxial huge mass causing compression of the brain (Fig. 1). Fine-needle aspiration biopsy of the mass confirmed the diagnosis of plasmacytoma consisting of atypical plasma cells. Bone-marrow aspiration revealed plasma cell infiltration and relapse of the disease. The patient refused surgery and the tumor was treated with local irradiation followed by systemic chemotherapy of vincristine-carmustine-doxorubicine-prednisone. The mass and symptoms of diplopia and pain completely disappeared within 2 weeks, although a bone defect of 10 cm remained. He is still alive and controlled at regular intervals.

Plasmacytomas can occur in bone or extramedullary tissues as isolated lesions or during the course of multiple myeloma. Skull lesions of multiple myeloma are usually noted by osteolytic changes such as punch-out lesions. However, plasmacytoma of the skull may be a rare complication of this disease [2]. It may be a presenting symptom or a complication during the course of the disease, as in our case. Intracranial plasmacytomas must be differentiated from meningiomas and metastatic bony tumors. Surgery, radiotherapy, and chemotherapy, alone or in combination, may be used successfully in the treatment of plasmacytomas of the skull [3].

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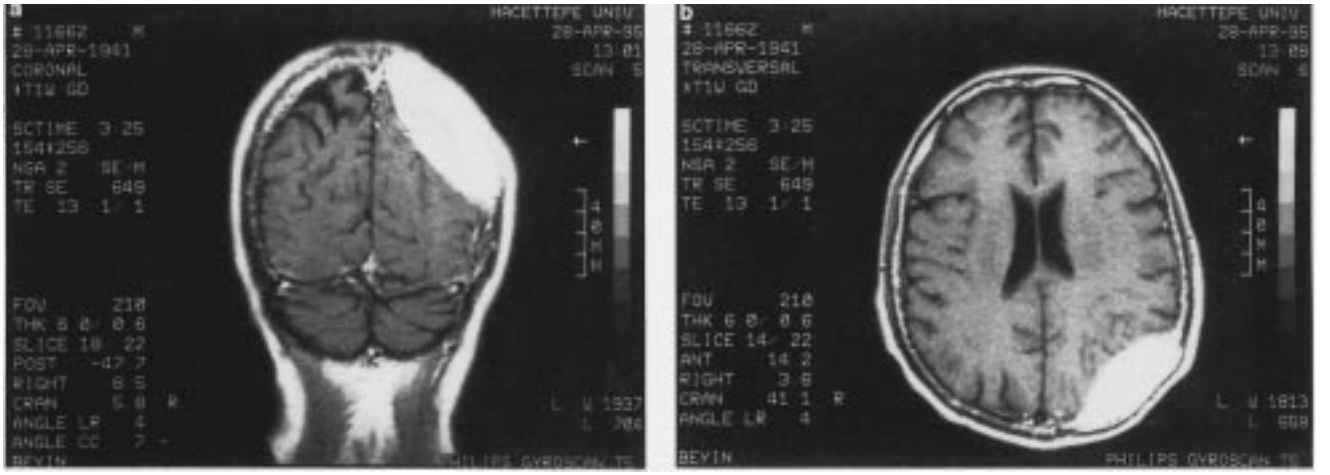

Fig. 1. Extraaxial bulky mass of the skull with intracranial involvement is shown in T1-weighted magnetic resonance coronal (a) and transverse (b) images with intense contrast enhancement.

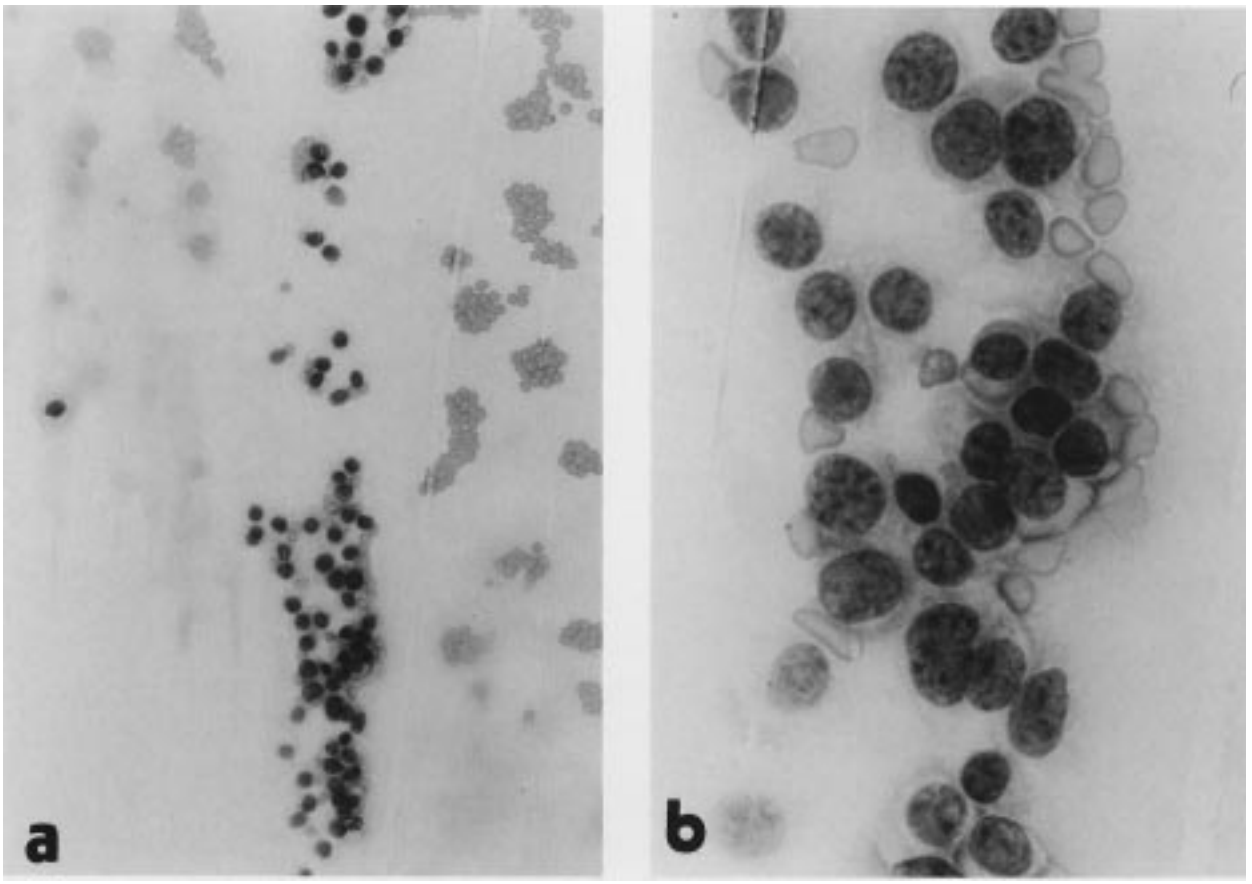

Fig. 1. a: Clumps of plasma cells in one of many streaks at the tail end of the blood smear. b: Higher magnification showing the nuclear pattern, and some cells with the Golgi zone.

Clumping of Plasma Cells: A Pitfall in the Diagnosis of Plasma Cell Leukemia

To the Editor: We recently encountered a case of secondary plasma cell leukemia (PCL) in which plasmacytosis was not detected by the automated cell counter. Peripheral blood smear was subsequently checked, and the white cell differential differed greatly between the manual and automated methods, because numerous clumps of plasma cells located at the tail end of the blood film were not accounted for by the automated cell counter. The number of plasma cells in the peripheral blood actually exceeded $2{,}000 \times 10^6$/l.

The patient was a 62-year-old Chinese woman previously diagnosed as having multiple myeloma based on the findings of 90% plasma cells in the marrow, monoclonal IgG 124 g/l, and an X-ray showing multiple lytic lesions. She responded to the standard oral melphalan/prednisone regime.

Two and a half years after the initial diagnosis of multiple myeloma, plasmacytosis recurred in the bone marrow. A complete blood count by a Coulter STK-S (Coulter, Miami, FL) showed the following: hemoglobin 8.2 g/dl, hematocrit 0.241, RBC 2.80×10^{12}/l, WBC 5.1×10^9/l (neutrophils 61.3%, lymphocytes 29.5%, monocytes 7.6%, eosinophils 1.0%, and basophils 0.6%), and platelets 40×10^9/l. The white cell histogram was compatible with the above data, with no abnormal tracing. There were flags for anemia and thrombocytopenia only.

When the peripheral blood smear was microscopically examined, however, the WBC differential was quite different from the above (neutrophils 23%, lymphocytes 12%, monocytes 5%, and plasma cells 60%), due to numerous clumps of plasma cells present at the tail end of the smear (Fig. 1).

A diagnosis of both primary and secondary PCL relies solely on the presence of a large number of plasma cells in the peripheral blood. In this case, even though the number of plasma cells fulfilled the diagnostic criteria, the fact that they were clumped presented a diagnostic pitfall.

The plasma cell clumps were probably excluded from reading by the automated cell counter because their size exceeded the upper threshold of detection in the WBC channel. There was no flagging by the counter to alert us to an abnormal white cell subpopulation. Because of thrombocytopenia recorded by the counter, we checked the blood film of this patient to verify the platelet count and to look specifically for platelet clumping. Serendipity led to the discovery of plasma cell clumping, at the tail end of the blood smear not customarily closely examined for verifying platelet count or white cell differential.

In vitro clumping of blood cells other than red cells and platelets has been described, albeit infrequently. In vitro granulocyte aggregation was first reported by Epstein and Kruskall [1], and then by Rohr and Rivers [2] and Deol et al. [3]. Lymphoma cells were found to form clumps in the peripheral blood by Juneja et al. [4], and more recently by Imbing et al. [5]. Clustering of lymphocytes in a case of chronic lymphocytic leukemia was reported by Bizzaro and Piazza [6].

Clumping was thought to be an in vitro phenomenon, because it could be avoided or aborted by different maneuvers. We obtained blood from the patient in K_3EDTA, citrate, and heparin, and prepared blood films both at room temperature and at 37°C, but clumping of plasma cells persisted. We did not obtain blood by finger stick.

In vitro clumping of plasma cells is a heretofore unreported phenomenon.

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It's Time to Define "EBV-Associated Lymphomas"

To the Editor: Oshima et al. [1] report evidence of Epstein-Barr virus (EBV) infection in nearly 50% (52 of 106) of non-Hodgkin's lymphomas (NHLs). However, they refrain from addressing them as "EBV-associated lymphomas." In only 13 of their 106 NHLs, EBV^+ tumor cells constituted $>2\%$ of cells on in situ hybridization (ISH). Though not specifically mentioned, it is likely that these cases were positive by Southern blotting (SB). In the other 39 cases, $<2\%$ of lymphoid cells were positive. In such cases, identifying $EBER\text{-}1^+$ cells as tumor cells and not as nontumoral bystander cells would be difficult. The task would be impossible in at least 17 cases, which were follicular small cleaved and diffuse small cleaved lymphomas. It is likely that these cases would have been negative by SB, but could have yielded positive results by polymerase chain reaction (PCR).

The questions that we need to address are: 1) How do we make a diagnosis of an "EBV-associated lymphoma?" and 2) What is the role of PCR in the study of EBV association?

"EBV-associated lymphomas" can be recognized by 1) presence of monoclonal episomal EBV as demonstrated by SB with a terminal repeat (TR) probe, and 2) ISH with the EBER-1 probe or immunohistochemistry for LMP-1, where most tumor cells are positive [2,3]. All "EBV-associated lymphomas" may not necessarily meet these criteria. In lymphomas, where EBV^+ cells are fewer, it should be ensured that the cell giving the signal is neoplastic. Fewer EBV^+ cells in a lymphoma could imply a) EBV^+ reactive cells, b) downregulation of EBER-1 in a proportion of cells, c) loss of the EBV genome by the tumor cells, or d) EBV infection following neoplastic transformation [4]. In NHLs with a large cell component, EBV association can be identified by performing ISH and immunophenotyping on the same section or on serially cut sections. Positive cells should have the corresponding immunophenotype and morphologic features of neoplasia. Obtaining a weak positive signal on SB with the *Bam*HI W-region probe or finding an amplified EBV product by PCR is not sufficient for a diagnosis of "EBV-associated lymphoma." Evaluation by PCR can yield additional information regarding the EBV subtype and mutations in the EBV genes which can accentuate their oncogenic potential [3,5].

Investigating EBV association involves addressing pathogenetic relationships. The value of such studies could be diluted by including cases which have EBV^+ bystander lymphoid cells. In the study of Oshima et al. [1], the frequency with which $<1\%$ of EBV^+ lymphoid cells were seen was similar in lymphomas and in nonspecific lymphadenitis.

In conclusion, one should be skeptical about EBV association 1) if an NHL has <5–10% of EBV^+ lymphoid cells, or 2) if positivity is based a) solely on PCR, b) on a weak signal on SB with a *Bam*HI W-region probe, or c) on finding oligoclonal or polyclonal EBV on SB with a TR probe.

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Thrombotic Thrombocytopenic Purpura Caused by Ticlopidine, Successfully Treated by Plasmapheresis

To the Editor: Thrombotic thrombocytopenic purpura (TTP) is a rare disorder characterized by thrombocytopenia, microangiopathic hemolytic anemia, renal dysfunction, neurological abnormality and fever [1]. Since the introduction of plasmapheresis and plasma infusion for treatment of TTP, dramatic improvement in disease prognosis has been obtained in approximately 80% of patients. However, the disease remains fatal in the remainder [1]. TTP can be idiopathic or secondary in association with infections, connective tissue disorders, tumors, and drugs [1]. Antiplatelet agents are increasingly used for prevention of thrombotic events, and ticlopidine is one such drug. In recent years, some cases of TTP caused by ticlopidine administration have been reported [2], while TTP cases from other causes that were successfully treated by ticlopidine have also been reported [3]. These opposing effects of ticlopidine generated suspicion concerning the existence of ticlopidine-induced TTP. We report on a case of TTP presumably caused by ticlopidine administration which was successfully treated by plasmapheresis.

A 77-year-old female complained of dizziness and was administered ticlopidine, 200 mg/day, and berahistine since December 28, 1995. On January 22, 1996, she was hospitalized complaining of diarrhea, abdominal discomfort, and progressive severe general fatigue. Laboratory examination on admission revealed hemoglobin 11.7 g/dl, WBC 9,000/μl, platelet $1.0 \times 10^4/\mu l$, fragmented red cells in the peripheral blood smear, normal bone marrow, negative Coombs tests, total bilirubin 4.1 mg/dl, indirect bilirubin 2.9 mg/dl, LDH 3,056 IU/l, creatinine 2.3 mg/dl, and BUN 79.6 mg/dl. She became drowsy, confused, and comatoase on the following day. All drugs were withdrawn. Plasmapheresis was performed from the second day of admission, 3,200 ml for 3 days and 2,400 ml for 1 day. She regained consciousness after 3 days, and platelet count was normalized after 4 days. The patient recovered completely with no residual abnormality and no sign of relapse during 3 months of follow-up.

The pathogenesis of TTP remains unknown, and might have been initiated by endothelial cell damage in the progression of intravascular platelet aggregation, and might include several mechanisms: 1) endothelial cell

injury by causative agents, e.g., bacterial endotoxins, verotoxins, antibodies, immunocomplexes, and drugs; 2) decreased capacity to form prostacycline (PGI2), which is a potent inhibitor of platelet activation synthesized by the vascular endothelium; and 3) abnormal von Willebrand factor (vWF) processing, in which unusually large vWF multimers are formed in the plasma of patients with relapsing TTP, enhancing binding to activated platelets [1,4].

Several agents that cause TTP are known, including antineoplastic agents, contraceptive agents, antibiotics, and cyclosporine [1]. There have been more than 10 reported cases of TTP associated with ticlopidine administration [2]. In all these cases, there were no other causes of TTP to be considered, as in our case. The mechanism by which ticlopidine causes TTP is unknown. It does not inhibit platelet cyclooxygenase or prostacyclin synthetase, so that prostacyclin production is not affected, nor does it modify cAMP concentration, so that adenylate cyclase is not stimulated [5]. Ticlopidine affects aggregation induced by both collagen and ADP, and fibrinogen binding to glycoprotein complex IIb/IIIa is impaired [5]. Recently, abnormalities in vWF multimers were observed in drug-associated TTP in patients receiving cyclosporine and chemotherapeutic agents [6]. From our experience, we think that ticlopidine could cause secondary TTP, as well as the well-known adverse effects of cytopenias. Careful monitoring of hematological data is necessary during administration of ticlopidine.

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Specific Cutaneous Involvement Indicating Relapse of Burkitt's Lymphoma

To the Editor: Commonly, Burkitt's lymphoma presents with large extranodal tumors affecting facial bone, abdominal disease, and central nervous system involvement [1]. Specific cutaneous lesions in Burkitt's lymphoma seem to be very unusual. We report on the case of an HIV-negative patient with Burkitt's lymphoma in whom cutaneous involvement revealed relapse of the disease.

A 43-year-old Polynesian man was hospitalized in our institution in January 1995 for treatment of Burkitt's lymphoma stage I, diagnosed on biopsy of a left inguinal lymph node inducing large lymphedema of the lower limb, showing typical features of Burkitt's lymphoma and no evidence of Epstein-Barr virus DNA by in situ hybridization. Physical examination was otherwise normal. No Burkitt's cells were detected in peripheral blood. The serum lactate deshydrogenase level was 1.5-fold normal value. Cerebral spinal fluid analysis and bone-marrow biopsy were unremarkable. HIV antibodies were not detected. The patient was treated with three courses of chemotherapy combining methotrexate, cyclophosphamide, vincristine, adriamyicn, and prednisone. Intrathecal methotrexate for central system prophylaxis was also administered. A 45-gray radiotherapy of the left inguinal node was associated with the second course of chemotherapy. The patient was then evaluated and considered to be in complete remission. In April 1995, while he was receiving consolidation courses with methotrexate and cytarabine, 10 asymptomatic, firm, and well-demarcated erythematous nodules, 1–2 cm diameter, appeared on the left thigh. No inguinal lymph node was found. Histopathologic examination and immunohistochemical staining of a nodule revealed a diffuse and dense infiltrate of Burkitt's cells in the dermis and subcutaneous tissue with a Grenz zone, indicating Burkitt's lymphoma, cutaneous localization. No leukemia cells were observed on peripheral blood, and bone-marrow biopsy was always unremarkable. Two weeks later, a left inguinal lymph node was found. Monthly courses with cytarabine, methotrexate, and prednisone were administered without any improvement on the inguinal lymph node and cutaneous nodules. The patient was lost to follow-up.

Specific cutaneous involvement in Burkitt's lymphoma seems to be a very rare event, and only isolated cases have been reported [2–4]. Since 1986, Burkitt's lymphoma has been diagnosed in 26 patients in our department, and this patient is the only one in whom specific skin lesions occurred. Skin invasion in leukemia and lymphoma is usually considered to result from blood dissemination of malignant cells. On the contrary, in our patient, lesions seem to have resulted from local invasion. Indeed, the cutaneous lesions were exclusively located in connection with the involved lymph node, and peripheral blood and bone-marrow involvement was never observed, even at the time of skin-lesion development. Of note, local invasion has been described at the site of insertion of catheter tracts or of celioscopy [5]. Interestingly, cutaneous lesions indicated relapse of the disease. Although cutaneous involvement seems to indicate widespread multiorgan involvement in the study by Banks et al. [2], this case demonstrates that other pathogenic means of skin invasions can occur without necessarily signifying general disease.

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Microcytic Anemia With Iron Malabsorption

To the Editor: I read with interest the article entitled "Microcytic Anemia With Iron Malabsorption: An Inherited Disorder of Iron Metabolism" by Hartman and Barker which appeared in the April issue [1]. The patients albeit children did remind me of the syndrome described in elderly women in 1967 [2].

The patients reported in 1967 had hypochromic hypoferremic anemia with adequate iron in their bone marrow and no evidence of malignancy or inflammation. Erythrokinetic studies were responsible for the understanding of the mechanisms behind the anemia. Plasma iron turnover and iron red cell *utilization* (both measured by intravenous injection of inorganic radio-active iron that binds to transferrin and goes mainly to the bone marrow for hemoglobin synthesis) were normal indicating that total and effective erythropoiesis were normal. Red cell iron *reutilization* was very low. The latter was measured by intravenous injection of radio-active iron tagged hemoglobin solution (organic radioactive iron which first is picked up and processed by the reticuloendothelial system [RES] is released to the circulation for hemoglobin synthesis and appear in the red cells over a 3-week period). Radio-active iron absorption was almost nil. The diagnosis was "primary defective iron reutilization" which means iron released from hemoglobin was trapped in the RES and its delivery to the circulation was poor. The patients responded well to testosterone enanthate therapy. It was felt that the hormone mobilized iron from the RES. Currently, the anemia of two elderly women with the same diagnosis responded well to Danazol (Besa, E., personal communication).

I suspect that the authors did not perform erythrokinetic studies on their patients because of their age. The two children reported had little to no iron in their bone marrows. This could be due to the fact that they had no chance to replete their marrows since their iron absorption was poor from birth. This fact might also be responsible for decreased serum ferritin in the presence of poor iron release from the RES (which increases serum ferritin). We have observed lower levels of serum ferritin than expected in patients with anemia of chronic disease who happened in addition to have iron defeciency. It is interesting that the defect was inherited. I would recommend, in case their anemia gets worse, Danazol treatment after a course of iron dextran therapy. Dextran iron will replete iron stores and Danazol hopefully will release it to the circulation for hemoglobin synthesis by red cells precursors.

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